UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/491,500	01/26/00	BLACK K	CEDAR043-453

HM12/1220

SIDNEY & AUSTIN
A PARTNER INCLUDING PROFESSIONAL CORPORA
555 WEST FIFTH STREET
LOS ANGELES CA 90013-1010

EXAMINER	
NIKODEM,D	
ART UNIT	**PAPER NUMBER**
1633	6

DATE MAILED: 12/20/00

Please find below and/or attached an Office communication concerning this application or pr c eding.

Commissioner of Patents and Trademarks

Files

Office Action Summary	Application No. 09/491,500	Applicant(s) BLACK ET AL.	
	Examiner David Nikodem	Art Unit 1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 September 2000* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-34 and 97-109* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-34 and 97-109* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

R sponse to amendment

1. Applicant's amendment and response to the official Office Action mailed June 20, 2000 as Paper No. 3, has been received and filed on September 25, 2000 as Paper No. 4. Claims 101, 104 and 108 have been amended, claims 35-96 have been canceled. Claims 1-34 and 97-109 are pending.

2. Applicant's arguments filed September 25, 2000 have been fully considered but they are not persuasive. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 103

3. Claims 1-34 and 97-109 stand rejected under 35 USC § 103 for reasons of record. Applicant's arguments have been fully considered but they are not persuasive.

4. Firstly, with regard to motivation, applicant argues (page 6) that no motivation existed to modify the method of Black. Examiner disagrees. Applicant argues that Black fails "to teach that bradykinin and its analogs are potassium channel agonists." Applicant further argues that no reference was known at the time of filing that disclosed the potassium channel agonist properties of bradykinin and its analogs. Examiner disagrees. As previously argued, the reference of record, Sobey, *et al.* teaches that vasodilator responses

of cerebral arterioles to bradykinin involve the activation of potassium channels. This is direct evidence that bradykinin is an agonist of potassium channels and increases potassium ion flux and potassium ion concentrations.

5. Further, applicant argues that Black failed to disclose a mechanism for bradykinin induced permeability increase in abnormal capillaries and that the hindsight in the instant application is necessary to utilize potassium channels in increasing the permeability of abnormal brain microvasculature. Examiner disagrees. Although Black does not teach the mechanism of bradykinin, the prior art reference Sobey, *et al.* does. As previously argued, it would have been obvious for one of skill in the art to investigate other potassium channel agonists, similar to bradykinin, in order to determine if a similar effect is seen - namely that of increasing potassium ion flux and potassium ion concentrations in abnormal brain vasculature.

6. Further, applicant states that "applicant is unaware of any references available at the t time the present specification was originally filed that linked vasodilation to the permeability of abnormal brain capillaries, *in vivo*." Examiner disagrees. Black teaches (page 1, line 47) that "bradykinin is a very powerful vasodilator." Black further teaches that bradykinin increases the permeability of the blood brain barrier in abnormal brain tissue." This is a direct link between the two mechanisms of bradykinin, which applicant states, have not been shown to be related. Black states (page 1) that "there is a continuing need to develop methods for selectively opening abnormal brain tissue capillaries in order to allow selective passage of neuropharmaceutical agents into abnormal brain tissue

without increasing the permeability of the normal blood-brain barrier." Thus, the motivation does exist in Black to utilize other chemicals and/or compounds that may have the same effect(s) as bradykinin.

7. Secondly, with regard to expectation of success, examiner disagrees with applicant's arguments. In view of the effect of bradykinin disclosed in Black and the teaching of Sobey, *et al.* to the mechanism of bradykinin and the teaching of a multitude of other bradykinin-like agonists by Cherksey, one of skill in the art would have expected some degree of success by other potassium channel agonists. The rejection is a 103 type rejection and the combination of the references does suggest to one of skill in the art to expect a degree of success using other potential agonists.

8. Thirdly, with regard to the failure of the references to suggest all the limitations of the claims, examiner disagrees with applicant's arguments. Applicant argues that the references fail to teach "administering to a mammalian subject having an abnormal brain region a potassium channel agonist, other than bradykinin or a bradykinin analog in conjunction with administering to the subject simultaneously or substantially simultaneously with the potassium channel agonist a medicant." The arguments submitted in the previous Office action address this argument. Briefly, the rejection is a 103 obviousness rejection. All the limitations of the claims do not have to be found in one reference, but merely have to be obvious from a combination of references so as to assert *prima facie* obviousness that one of skill in the art would have been motivated to combine the teachings of the references.

9. With regard to a kit – the lack of instructions does not render a kit as non-obvious. It would be obvious to any one of skill in the art to add an instruction manual to a method that is being marketed commercially.

10. Note that the rejections are based on the knowledge of one of skill in the art, namely scientists that are familiar with the field and that have experience designing and implementing experiments. A certain degree of consideration to this fact is necessary when examining the claims for 103 rejections with regard to the motivation and expectation of success.

Double Patenting

11. Claims 1-5, 7-9, 11, 12, 14-22, 24-26 and 28-34 stand rejected under the doctrine of obvious type double patenting for reasons of record. Applicant's arguments have been fully considered but they are not persuasive. Applicant's arguments are based on the same facts presented in the 103 rejection rebuttal. Examiner has addressed these arguments above and reiterates those arguments here. The double patenting rejection stands.

<u>New</u> Claim Rejections - 35 USC § 112

12. Claims 1-34 and 97-109 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such

a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

13. The claims are drawn to a method of delivering a medicant to an abnormal brain region in a mammal comprising administering a potassium channel agonist, other than bradykinin or a bradykinin analog, under conditions that increase potassium flux, and/or increase permeability of arterioles or capillaries that deliver blood to the abnormal brain region, and the simultaneous delivery of said medicant so that said medicant is selectively delivered to cells of said abnormal brain region. The claims are further drawn to limitations of the broad breadth of the above method, including, type of abnormal brain region (stroke-affected, ischemia-affected, tumor, *etc.*), type of medicants (diagnostic agents, cytokine, nucleotide analog, *etc.*), type of delivery (intracarotid injection, intraarterial injection, *etc.*), dosages (0.075-1500 μg/Kg, *etc.*), type of mammal (human, canine, feline, *etc.*), and rates of delivery (μg/Kg,min, *etc.*). The claims are further drawn to pharmaceutical compositions and kits comprising a potassium channel agonist, other than bradykinin or a bradykinin analog, formulated for intravascular infusion or injection with said medicant. The aforementioned limitations upon the medicant, the agonist, type of abnormal brain region, type of mammal, type of dosage, and rates of delivery apply for the pharmaceutical compositions. Further limitations upon the pharmaceutical compositions include an acceptable buffer solution, including phosphate buffered saline. Limitations upon the kit include instructions and the aforementioned types of agonist.

14. Note that the enablement rejection is directed towards the intended use of the method of delivery and the intended use of the pharmaceutical composition. The specification is directed entirely towards using the claimed method and/or the pharmaceutical composition for treatment of a disease or disease state. When the claims are read in light of the specification, the claims have as the sole implied, intended use, treatment, since the specification is not directed towards any other intended use. The only asserted utility is for treatment or eliciting a treatment effect. Further, a pharmaceutical composition, by definition, reads on treatment (as opposed to a composition).

15. The specification fails to teach any treatment or show any treatment effect of any disease, disease state or pathology. The art of drug delivery and eliciting a treatment effect is an unpredictable art. Many factors affect the delivery of drugs to specific regions of the body. For example, Sabate, *et al.* teaches that the blood brain barrier prevents access to the brain of numerous macromolecules of therapeutic value. Delivery of such molecules requires intracerebral or intracerbroventricular injection, and infusion using osmotic pumps when long-term treatments are necessary. Therefore, the combination of infectious risks and constraints of the delivery technique have precluded the generalized use of drugs. Further, it would be unpredictable as to which drugs would elicit a treatment effect for which diseases when used in combination with specific drugs to permeabilize the microvasculature, specifically that in the brain.

16. Further, it is unpredictable in the art as to what pharmaceutical compositions actually will have a therapeutic effect, *in vivo*. It is well known in

the art that a variety of factors need to be taken into consideration for the delivery and elicitation of an effect by pharmaceutical compositions, including: formulation, method of delivery, site of delivery, composition uptake, composition half-life, and composition concentration and efficacy. It would require undue experimentation for one skilled in the art to identify and test all pharmaceutical compositions for an effect and thus, only those pharmaceutical compositions that are identified and enabled in a disclosure carry patentable weight.

17. It would require undue experimentation for one of skill in the art to practice the invention as claimed. The amount of experimentation would require the *de novo* trial and error experimentation to determine the elicitation of a treatment effect with which medicants when delivered in combination with which drugs that increase capillary permeability. Further, different combinations of medicants and permeabilizing drugs will have different degrees of effect; it is unpredictable which combinations will give a treatment effect. In view of such, one of skill in the art would not be able to practice the invention as claimed. Thus, the invention is not enabled.

18. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Nikodem whose telephone number is (703) 308-8361. The examiner can normally be reached on M-F, 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Clark can be reached on (703) 305-4051. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-8724 for regular communications and (703) 308-8724 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1123.

David Nikodem
November 29, 2000

Deborah Clark
DEBORAH J. R. CLARK
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600